DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/30/2007 has been entered.

Claims 1-44, 47-61, 63-69, 71-77, 79-93, and 95 have been cancelled. Claims 101-104 have been withdrawn. Claims 105-110 are new. Claims 45 and 62 have been amended.

Claims 45, 46, 62, 70, 78, 94, 96-100, and 105-110 are under examination.

2. The rejection of claims 45, 46, and 98 under 35 U.S.C. 102(b) as being anticipated by Gavin et al. is withdrawn in response to Applicant's amendments to the claims filed on 02/26/2008.

The rejection of claims 45, 46, and 98 under 35 U.S.C. 112, first paragraph, as introducing new matter, is withdrawn in response to Applicant's amendments to the claims filed on 02/26/2008.

Specification

3. The claim listing is objected to because it does not indicate the correct status of the claims 101-104. It is noted that claims 101-104 have been withdrawn (see the final Office action of 10/04/2007), however their status is indicated as "previously presented". Appropriate correction is required.

4. The use of the trademarks Dyna beads, GalScreen, NorthStar, and NautScan have been noted in this application (p. 21, line 29; p. 44, lines 18, 20, and 25). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, written description

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 45, 46, 62, 70, 78, 94, 96-100, and 105-110 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention.

See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Claims 45, 46, 62, 70, 78, 94, 96-100, and 105-110 are drawn to nucleic acid molecules encoding mutant AAV proteins with increased activity, wherein the increased activity results in increased virus titer. Therefore, claims 45, 46, 62, 70, 78, 94, 96-100, and 105-110 encompass a wide and variable genus of nucleic acid molecules the structure of which is not sufficiently disclosed in the specification and the claims.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude the inventors had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing

distinguishing identifying characteristics sufficient to show that the Applicants were in possession of the claimed invention (January 5, 2001, Fed. Reg., Vol. 66, No. 4, pp.1099-11). In analyzing whether the written description requirement is met for the genus claims, it is determined whether representative numbers of species have been described by their complete structure and functional characteristics.

When the claims are analyzed in light of the specification, the mutant nucleic acid can be any nucleic acid encoding a mutant Rep protein, as long as the Rep protein has increased activity (p. 9, paragraph 0111, p. 10, 0133, p. 16, paragraphs 0195-0200, p. 23, paragraph 0208). The genus of nucleic acids encoding mutant Rep proteins is very large; and a great deal of variability is encompassed by the instant claims. The instant claims encompass in their breadth any nucleic acid encoding for a mutant Rep protein that has increased activity. With the exception of the sequences disclosing eight mutations resulting in increased replicative activity (see the Table on p. 46-46), the specification fails to describe additional representative species of the nucleic acids mentioned above. The genus (i.e., the nucleic acids encoding for mutant Rep proteins) is described by its function to affect viral replication, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different nucleic acids. Applicant has not provided any information besides the characterization of the genus as having increased activity, wherein the increased activity results in increased viral replication. This limited

characterization, however, does not indicate that the Applicant had possession of the claimed genus of modified nucleic acids. Applicant is relying upon biological activity and the disclosure of eight mutants having increased activity to support an entire genus. It is well known that minor structural differences among even highly structurally related compounds can result in substantially different biology. The specification fails to disclose what requirements a nucleic acid must meet to encode a mutant Rep protein with increased activity, i.e., the specification fails to provide the relationship between structure and function for the nucleic acids encoding the mutant proteins. The specification does not contain any disclosure of the structure of all variants. One skilled in the art would know that a change of even one amino acid residue in the claimed sequences could render an inactive protein or a protein with a diminished activity. Therefore, Applicant has not disclosed the requisite structural features of the protein that result in the disclosed increased activity, a feature deemed essential for the instant invention. Therefore, one of skill in the art would not recognize Applicant to be in possession of the entire genus of nucleic acids encoding a mutant Rep protein.

Applicant argues that the application identifies and provides examples of at least 6 species of nucleic acid molecules encoding mutant Rep proteins that when expressed result in AAV with higher titer. Applicant submits that the specification provides detailed description how to isolate and prepare additional species that have the requisite property. In addition, Applicant argues, the specification describes preparation of and testing and the results of testing of all hundreds of species in which each amino acid

was replaced one-by-one with alanine to identify hits, and then each hit replaced in turn with every other amino acid to identify hits that have the property of increased titer. Hence, Applicant argues, he likely ferreted out all of the residues that can be mutated to exhibit increased titer and, if any are missing or if there are other combinations, the specification clearly teaches how to identify other such mutants. With regard to the various serotypes, Applicant argues that they are allelic variants with minimal variation; the specification identifies the residues in each of these variants that can be modified to exhibit increased AAV titer. Applicant points out that there is no requirement in patent law to provide working examples of every single species within a claim. Applicant argues that he tested every position, one-by-one, in the Rep proteins and identified those which alter AAV titer, and, for those, identified amino acid replacements that result in increased titer. Further, the specification even identifies the corresponding mutations in the highly conserved serotypes. In view of the specification, the skilled artisan is directed to positions to be modified, and is taught, in detail, how, if needed, to identify any other positions. There is no structural feature that can be identified; the instant claims are not directed to an improved doorknob, but to modified proteins, whose structure is based on its constituent amino acids. As discussed previously, the application describes more than a representative number of species by actual reduction to practice, the application provides the results of testing every residue to identify those that alter titer, and to identify specific replacements that result in increased viral titer. The specification provides the sequences of such molecules and corresponding positions in other AAV serotypes. The application tested every amino acid locus to

identify all whose change results in a change in titer. Every replacing amino acid was tested. Hence the application provides a detailed description of the relationship between the structure and functioning of Rep proteins as assessed by assessing viral titer. Based on this property and using the methods described, the application teaches how to identify any additional species within the scope of the claim and how to assay or test combinations of mutations. The application describes a method for preparing proteins that have predetermined properties and exemplifies it using the AAV Rep proteins. In fact, the application exemplifies an entire genus with respect to one serotype and identifies the corresponding mutations in all other AAV serotypes. Thus, Applicant possessed the claimed subject matter at least as of the filing date of the instant application. Applicant submits that the claimed nucleic acid molecules are sufficiently described based on an identifying characteristic shared amongst the genus of claimed molecules, i.e. the feature of increased viral replication. The specification describes in great detail how to identify such molecules, and exemplifies representative species, including their sequence, that exhibit this identifying feature. Applicant is providing mutants that have increased activity as manifested by increased viral titer. The application tested every single position, using every amino acid replacement at each locus, in one serotype and tested the effect on the resulting AAV viruses. Hence for AAV-2, every member of the genus is identified and tested. The application was prepared and tested every combination of modified amino acid (see, e.g., the Example and Figures) for each of the Rep proteins and identifies the loci that contribute to changes in viral titer. The application further identifies those loci and amino acid

changes the result in increased titer. Further, the application identifies the corresponding loci in all AAV serotypes. In addition, the application teaches how to prepare additional mutants and test them. The application provides the structure/function relationships.

The specification, including the Example, describe the testing of a variety of nucleic acid molecules encoding mutant Rep proteins and exemplify 12 clones having increased activity as manifested by increased viral replication (see e.g. Figure 2B). The specification describes the corresponding position of the encoded mutations in each of the seven AAV serotypes. The specification clearly describes that other mutants and other combinations of mutants can be generated and identified. For example, the specification at page 33, lines 3-8 states:

> Other combinations of mutations can be prepared and tested as described herein to identify other leads of interest, particularly those that have increased rep protein activity or that result in higher viral titers in cells containing such viruses that include appropriate cis acting elements for viral production.

Hence, the instant application clearly describes a genus of nucleic acid molecules encoding mutant Rep protein having a relevant identifying characteristic of increased activity as manifested by effects on increased viral titer. Because the specification adequately describes how one may (i) identify and select molecules that provide increased activity; (ii) generate the molecules; and (iii) measure a specific effect, namely effects on increased viral titer, Applicant had possession of the claimed subject matter at the time of filing the application.

The specification exemplifies more than a reasonable number of species Applicant is not required to provide a representative of everything claimed but may show possession by providing identifying features common to all members. As described above, Applicant, by way of detailed descriptions of features, working example, and exemplary molecules, has done exactly that. Accordingly, Applicant respectfully submits that the specification sets forth a representative number of species of the claimed nucleic acid molecules, which species were actually reduced to practice, to evidence Applicant's possession of the claimed subject matter. The specification provides 12 loci in nucleic acids encoding mutant Rep proteins, that result in increased viral titer, sets forth corresponding mutations in each of the other AAV serotypes, thereby providing no less than 70 species of nucleic acid molecules encoding a mutant AAV Rep protein that have increased activity. This is based on testing and exemplifying 566 species. Applicant argues that what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Applicant submits that one of skill in the art would conclude that, having tested all combinations of mutations and provided the data for such tests the description in the specification constitutes a sufficiently detailed description to evidence, that Applicant's possession of nucleic acid molecules that encode Rep proteins that result in increased titer compared to wild-type under standard conditions. Applicant argues that

the Examiner failed to indicate why one of skill in the art, who is in possession of the nucleic acid molecules encoding any one or more mutant Rep protein (via the overlapping nature of the reading frames), in view of the description in the specification of all of the tested species, including the Example, Figures 2 and Figures 3, which exemplify the sequence identity among AAV serotypes and corresponding positions, and of the methods for preparing and testing polypeptides for activity, in view of the extensive knowledge of those of skill in the art, would be unable to recognize, upon reading the disclosure, that Applicant has possession of the claimed subject matter at least on the day of filing of the priority application. The specification clearly exemplifies mutations in the AAV genome that result in increased viral titer and teaches in great detail how to generate other such species. As discussed above, the specification describes testing of every amino acid along the length of each Rep protein to identify which residues alter titer, and then replaced each such residue to identify replacing amino acids that result in increased titer. Hence, it is possible that Applicant identified virtually all of the species in the genus.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

The instant claims recite that the claimed mutations (i.e., in the Rep78 of the AAV-2 serotype) are introduced at the corresponding residues in the other serotypes, and the specification defines that a corresponding residue refers to an amino acid position based upon alignment to maximize sequence identity, as demonstrated in Fig.

3 A and B (p. 6, paragraph 0071). However, it is clear from Fig. 3 A and B that the different Rep proteins of the different serotypes have different lengths and therefore, the "corresponding residue" does not have the same position in all proteins. Referring to Figure 3A, position 350 of AAV-2 is indeed a T residue. In five of the other six serotypes, this position is occupied by an A. Thus, how could one of skill in the art assume that an A to N mutation in any of these serotypes would have the same activity as the exemplified T to N mutation? There is no assurance that these mutations would have the same type of activity. The mutations identified in the instant application to AAV-2 Rep are completely random and bear no reasoning for mutating the particular residues. Thus no structure function relationship exists between the identified mutations and the protein. In essence there is no apparent understanding why, for example the T to N mutation that is exemplified has the effect that it does. The art teaches that Rep proteins are divided into partially distinct functional domains that are spread throughout the protein length and that most mutations disrupt Rep function (Gavin et. al., J Virol, 1999, 73: 9433-9445, p. 9433, column 2; of record). Based on these facts, one of skill in the art would not reasonably conclude that the results obtained with the Rep78 of the AAV-2 serotype could be extrapolated to other serotypes. With respect to the different Rep proteins of AAV-2, they would possess the same T residue at this position, as the differences between them are due to differential promoter use and differential splicing, yet all four proteins use the same reading frame. Therefore, a T to N mutation in AAV-2 Rep 78 would necessarily lead to a T to N mutation is the other three AAV-2 Rep proteins. The question then becomes, would

each of the individual Rep proteins be expected to individually lead to an increase in viral titer? The specification teaches that "Rep 52 and 40, the two minor forms of the Rep proteins, do not bind to ITRs and are dispensable for viral DNA replication and site-specific integration" (page 3, line7- 9). Since Rep 52 and Rep 40 play no role in ITR binding, viral replication, or viral integration, absent evidence to the contrary, one of skill in the art would have no reason to conclude that any mutant Rep 52 or Rep 40 would be capable of leading to an increased viral titer. Again, there is no teaching in the specification and no finding in the prior art that would suggest that Rep 52 or Rep 40 would have the activity that leads to the increased viral titer seen in the T to N mutation at position 350 of Rep 78. Thus, the skilled artisan would not have reason to believe the inventors were in possession of the invention as broadly claimed.

Importantly Applicant argues that:

> As discussed above, the specification describes testing of every amino acid along the length of each Rep protein to identify which residues alter titer, and then replaced each such residue to identify replacing amino acids that result in increased titer. Hence, it is possible that Applicant identified virtually all of the species in the genus.

It is noted that, after testing every amino acid along the length of each Rep protein, only 8 mutations were identified by the instant specification as resulting in the claimed increased Rep activity. Therefore, Applicant's arguments above support the conclusion that the claimed genus only comprises the disclosed 8 species of mutant Rep proteins. While it is true that Applicant provides means for producing and testing additional mutant Rep proteins and nucleic acids and this can be accomplished by routine experimentation, both the art and the specification teach that the majority of

mutations result in Rep proteins exhibiting reduced or unchanged activity. Based on all of the above, one of skill in the art would not recognize that Applicant invented what is presently claimed and the rejection is maintained.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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